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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,257	11/04/2003	Brenda F. Baker	ISIS-5316	6115
27180	7590	06/21/2006	EXAMINER	
ISIS PHARMACEUTICALS INC 1896 RUTHERFORD RD. CARLSBAD, CA 92008			HILL, KEVIN KAI	
			ART UNIT	PAPER NUMBER
			1633	
DATE MAILED: 06/21/2006				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.		Applicant(s)	
	10/701,257		BAKER ET AL.	
	Examiner		Art Unit	
	Kevin K. Hill, Ph.D.		1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-75 is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) ____ is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☒ Claim(s) 1-75 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. ____. |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date ____. | 6) <input type="checkbox"/> Other: ____. |

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - I. Claims 1-75, drawn to a composition comprising a first oligomer and a second oligomer, wherein at least said first or said second oligomer includes two nucleosides having a non-phosphorous-containing internucleoside linkage, and a method of modulating the expression of a target nucleic acid in a host cell or animal, classified in class 514, subclass 44.

2. **Should Applicant elect Invention I, further group restriction is required under 35 U.S.C. 121.** Claims 1, 35 and 67 are generic to a plurality of disclosed patentably distinct oligomers that include at least two nucleosides having a non-phosphorous-containing internucleoside linkage. Applicant is required to elect a single disclosed internucleoside linkage recited specifically in Claims 11-31 and 43-63 for prosecution on the merits to which the claims shall be restricted. Therefore, election is required of Invention I and one of Invention I, inventive groups (a)-(t) below, wherein the non-phosphorous-containing internucleoside linkage is, specifically:
 - a) an ether linkage of the formula recited in Claims 11 and 43,
 - b) an allyl ether linkage of the formula recited in Claims 13 and 45,
 - c) an allyl sulfide linkage of the formula recited in Claims 14 and 46,
 - d) a formacetal/ketal linkage of the formula recited in Claims 15 and 47,
 - e) a sulfamate linkage of the formula recited in Claims 16 and 48,
 - f) a sulfonamide linkage of the formula recited in Claims 17 and 49,
 - g) a siloxane linkage of the formula recited in Claims 18 and 50,
 - h) an amide or thioamide linkage recited in Claims 19 and 51,
 - i) a cationic allylpolyamine linkage recited in Claims 20 and 52,

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- j) a guanidyl linkage of the formula recited in Claims 21 and 53,
- k) a linkage of one of the formulas recited in Claims 22 and 54,
- l) a linkage of one of the formulas recited in Claims 23 and 55,
- m) a linkage of the formula recited in Claims 24 and 56,
- n) a linkage of the formula recited in Claims 25 and 57,
- o) a linkage of the formula recited in Claims 26 and 58,
- p) a linkage of one of the formulas recited in Claims 27 and 59,
- q) a linkage of the formula recited in Claims 28 and 60,
- r) a linkage of the formula recited in Claims 29 and 61,
- s) a linkage of one of the formulas recited in Claims 30 and 62, or
- t) a linkage of one of the formulas recited in Claims 31 and 63.

Claims 1, 35 and 67 link Invention I, inventive groups (a)-(t).

Invention I, inventive groups (a)-(t) are distinct because,

Invention I, inventive groups (a)-(t) are unrelated. The non-phosphorous-containing internucleoside linkages are distinctly different in structure, as illustrated by the numerous variations of linear or branched carbon side chains, aromatic rings and heterocycles, each of which may or may not contain additional heteroatoms. Furthermore, these unrelated structures are not obvious variations of each other because one skilled in the art does not expect aromatic ring systems to have the same chemical properties as non-aromatic ring systems. Each of the non-phosphorous-containing internucleoside linkage radicals confers a unique, non-obvious property onto the oligomer that will directly impact the bioavailability, toxicity or bioactivity of the compound.

A search for a compound of the formula in Claim 22 would not be co-extensive with a search for a compound of the formula in Claim 15. Further, a reference rendering a compound of the formula in Claim 13 as anticipated or obvious over the prior art would not necessarily also render a compound of the formula in Claim 26 as anticipated or obvious over the prior art. Similarly, a finding that a compound of the formula in Claim 30 was novel and unobvious over the prior art would not necessarily extend to a finding that a compound of the formula in Claim

27 was also novel and unobvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed non-phosphorous-containing internucleoside linkage, even though this requirement is traversed. Failure to elect a non-phosphorous-containing internucleoside linkage from Invention I, inventive groups (a)-(t) above consonant with Applicant's elected Invention I, may result in a notice of non-responsive amendment.

Claims 1, 35 and 67 link Invention I, inventive groups (a)-(t). The restriction requirement between the linked inventions is subject to the nonallowance of the linking claim(s), Claims 1, 35 and 67. Upon the indication of allowability of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim(s) depending from or otherwise requiring all the limitations of the allowable linking claim(s) will be rejoined and fully examined for patentability in accordance with 37 CFR 1.104. Claims that require all the limitations of an allowable linking claim will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

Applicant(s) are advised that if any claim(s) including all the limitations of the allowable linking claim(s) is/are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory

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double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

3. **Should Applicant elect any of Invention I, inventive groups (h), (k), (l), (p), (s) or (t), a species restriction is required under 35 U.S.C. 121.** Currently, Claims 19 and 51, 22 and 54, 23 and 55, 27 and 59, 30 and 62, and 31 and 63 of this application are directed to a plurality of disclosed, patentably distinct formulas that prohibit proper examination of this claim. For each of Invention I, inventive groups (h), (k), (l), (p) or (s) above, restriction is required to one patently distinct, non-phosphorous-containing internucleoside linkage formula, specifically:

- A. If I(h) is elected, then elect one formula from the list recited in Claims 19 and 51.
- B. If I(k) is elected, then elect one formula from the list recited in Claims 22 and 54.
- C. If I(l) is elected, then elect one formula from the list recited in Claims 23 and 55.
- D. If I(p) is elected, then elect one formula from the list recited in Claims 27 and 59.
- E. If I(s) is elected, then elect one formula from the list recited in Claims 30 and 62.
- F. If I(t) is elected, then elect one formula from the list recited in Claims 31 and 63.

For each inventive group, the non-phosphorous-containing internucleoside linkage formulas are distinctly different in structure, as described above, and are not obvious variations of each other. A search for an amide group would not be co-extensive with a search for a thioamide group. Further, a reference rendering one formula in Claim 22 as anticipated or obvious over the prior art would not necessarily also render another formula in Claim 22 as anticipated or obvious over the prior art. Similarly, a finding that one formula in Claim 30 was novel and unobvious over the prior art would not necessarily extend to a finding that another formula in Claim 30 was also novel and unobvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another, it would be unduly burdensome for the examiner to search and examine all

the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed the non-phosphorous-containing internucleoside linkage formula, even though this requirement is traversed. Failure to elect a formula from Invention I, inventive groups (h), (k), (l), (p) or (s) above consonant with Applicant's elected Invention I, may result in a notice of non-responsive amendment.

Should Applicant elect any of Invention I, inventive groups (a)-(t), a species election is required under 35 USC 121. Currently, Claims 1, 35 and 67 of this application is generic to a plurality of disclosed, patentably distinct non-phosphorous-containing internucleoside linkages that prohibit proper examination of the claims comprising the formulas recited in Claims 11-31 and 43-63. Therefore, election is required under 35 U.S.C. 121 of one species moiety for each of the respective radicals consonant with Applicant's elected invention for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable.

- i) If I(a) is elected, then elect one species for R_1 from the list of species recited in Claims 11-12 and 43-44.
- ii) If I(d) is elected, then elect one species for each X and Y radical from their respective lists recited in Claims 15 and 47.
- iii) If I(e) is elected, then elect one species for each X and Y radical from their respective lists recited in Claims 16 and 48.
- iv) If I(f) is elected, then elect one species for R_3 from the list recited in Claims 17 and 49.
- v) If I(h) is elected, then elect one species for R from the list recited in Claims 19 and 51.
- vi) If I(j) is elected, then elect one species for R from the list recited in Claims 21 and 53.
- vii) If I(k) is elected, then elect one species for R^6 from the list recited in Claims 22 and 54.

- viii) If I(l) is elected, then elect one species for R' from the list recited in Claims 23 and 55.
- ix) If I(m) is elected, then elect one species for D and R₆ from their respective lists recited in Claims 24 and 56.
- x) If I(n) is elected, then elect one species for L₁, L₂, L₃ and L₄ from their respective lists recited in Claims 25 and 57.
- xi) If I(o) is elected, then elect one species for L₁, L₂, L₃, L₄, R₁, R₂, R₃, R₅ and R₆ from their respective lists recited in Claims 26 and 58.
- xii) If I(p) is elected, then elect one species for R and R_A from the respective lists recited in Claims 27 and 59.
- xiii) If I(q) is elected, then elect one species for R₁ and R₂ from their respective lists recited in Claims 28 and 60.
- xiv) If I(r) is elected, then elect one species for L₁, L₂, L₃, L₄, R, R' and R'' are each one species, respectively, from their respective lists recited in Claims 29 and 61.
- xv) If I(s) is elected, then elect one species for R_{1a}, R_{1b}, R_{2a}, R_{2b}, R_{3a}, R_{3b}, R₄, R₅, R₆, Z₁, Z₂, Z₃, and Z₄ from their respective lists recited in Claims 30 and 62.
- xvi) If I(t) is elected, then elect one species for E, G, J, R₃, R₄ and W from their respective lists recited in Claims 31 and 63.

The numerous variations in the number, position and type of heteroatoms, linear or branched carbon chains result in a vast genus of structurally unrelated molecules that are not obvious variations of each other because one skilled in the art does not expect a hydroxyl group to have the same chemical properties as a sulphur, fluoride or a C₇-C₁₄ alkaryl group. Similarly, one would not expect a heterocyclic radical group to have the same chemical properties as a hydrogen radical group. Each of the radical species moieties confers a unique, non-obvious property onto the non-phosphorous-containing internucleoside linkage that will directly impact the bioavailability, toxicity or bioactivity of the compound.

Given the breadth of the claimed, unrelated structures, a search for all possible species at each of the recited radical groups imposes an exceptional burden on the Office. A search for a benzoxy radical group would not be co-extensive with a search for an ester radical group.

Further, a reference rendering a C=O radical as anticipated or obvious over the prior art would not necessarily also render an aromatic ring as anticipated or obvious over the prior art. Similarly, a finding that an -OH was novel and unobvious over the prior art would not necessarily extend to a finding that SO₂CH₃ was also novel and unobvious over the prior art. Because these inventions are distinct for reasons given above, and because a search of one does not necessarily overlap with that of another species, it would be unduly burdensome for the examiner to search and examine all the subject matter being sought in the presently pending claims and thus, restriction for examination purposes as indicated is proper.

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election. Failure to elect species consonant with Applicant's elected invention may result in a notice of non-responsive amendment.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kevin K. Hill, Ph.D. whose telephone number is 571-272-8036. The examiner can normally be reached on Monday through Friday, between 9:00am-6:00pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



DAVE TRONG NGUYEN
SUPERVISORY PATENT EXAMINER

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.